CD19 Targeted Low-Dose Rituximab Is Effective in the Management of Refractory Phospholipase A2 Receptor Antibody-Associated Membranous Nephropathy

To the Editor: Varied dosing regimens of rituximab (RTX) have been successfully used in the management of primary membranous nephropathy (PMN).[1,2] An ideal RTX dose and the long-term adverse effect of a larger cumulative dose are not clear. CD19 levels are used to gauge the drug effect.[1] Economic viability is a major part of any new therapeutic regimen. Low-dose RTX (100 mg) has been successfully used in ABO incompatible renal transplant.[3] In the present study, we report a similar approach of CD19 depletion using 100 mg of RTX in the management of M-type phospholipase A2 receptor antibody ($aPLA_2R$)-associated PMN refractory, dependent on or intolerant to conventional immunosuppressive regimens recommended by Kidney Disease: Improving Global Outcomes.[4]

All the study subjects had $aPLA_2R$-related PMN. The mean duration of nephrotic syndrome before RTX therapy was 33.67 ± 19.76 (median 13, range 10–62) months. Before receiving RTX, all the patients had an immunosuppression-free washout period of minimum 3 months. The mean proteinuria, serum albumin, and creatinine were 12.06 ± 10.78 (median 7.59, range 2.30–31.00) g/d, 2.09 ± 0.95 (median 1.64, range 1.30–3.50) g/dl, and 0.81 ± 0.21 (median 0.80, range 0.60–1.10) mg/dl, respectively. Five (83.3%) study subjects had nephrotic range proteinuria (>4 g/d) and 1 (16.7%) patient had subnephrotic proteinuria (2.3 g/d) and was treated as he had anasarca with severe hypoalbuminemia (1.3 g/dl) and hypercholesteremia. All the study subjects (4 resistant to cyclophosphamide and steroids, 1 intolerant to tacrolimus treatment, and 1 with relapsing disease) were treated with 100 mg of rituximab (CD19 monitored on day 2 and at every 4- to 6-week interval). In subjects with no response at 6 months, further infusion and monitoring was stopped (extended follow-up continued). All the subjects achieved CD19 depletion (<1%) with a single dose of 100 mg of RTX. All the patients received maximal tolerable doses of angiotensin receptor blockers (systolic blood pressure achieved was <130 mm Hg in all the subjects) and atorvastatin; doses of angiotensin receptor blockers were stable during the entire study period. During RTX therapy, the patients received no other immunosuppressive therapy. At the end of 6 months, 3 (50%) achieved remission in proteinuria with normalization of serum albumin, and had maintained it until the last follow-up (Table 1). All the subjects in clinical remission also had serological remission and nonresponders had persisting $aPLA_2R$ (Table 1). The mean time for CD19 reconstitution was 2.17 ± 1.17 (median 2, range 1–4) months. A total of 16 additional doses of RTX were required (mean 2.67 ± 0.82, median 2.5, and range 2–4).

Low-dose RTX has been successfully used in ABO incompatible renal transplant. Nakao *et al.*[3] reported successful use of 100 mg of RTX in 9 ABO incompatible renal transplant, with no difference in survival rates between low versus standard dose. Low dose of RTX has also been successfully evaluated in refractory rheumatoid arthritis.[5] Shenoy *et al.*[5] evaluated the therapeutic response of 100 mg of RTX in 14 patients with active rheumatoid arthritis; 58% and 42% of the patients achieved good and moderate response at 24 weeks, respectively. Seventy-nine percent of the patients achieved CD19 depletion (<0.01%) with single dose of RTX (100 mg). The CD19 depletion in the present study is better than that reported by Shenoy *et al.*; this may partly be explained by the difference in the definition of CD19 depletion (<1% and <5 cells in the present study vs. <0.01% in the study by Shenoy *et al.*).[5]

Ruggenenti *et al.*[1] studied RTX use in 100 subjects with PMN and reported a response rate of 56% (18 of 32 cases), when used as a second line agent. In the present study, the response rate of 50% was similar to that reported by Ruggenenti *et al.*[1] Ruggenenti *et al.* used a single dose of 375 mg/m^2 in all the patients compared with 100 mg with CD19 monitoring in the present study. Treatment protocol utilizing RTX in PMN widely varies among various centers; some prefer to use "extended protocol" of weekly (375 mg/m^2) RTX for 4 weeks,[6] whereas others choose to use CD19 targeted RTX infusion. Interestingly, most of the studies have demonstrated successful depletion of CD19 with a single dose, questioning the benefit of additional dosing, and many centers have evolved from "extended protocol" to "CD19 targeted dosing."[1,6] Assuming that CD19 depletion primarily translates to clinical response, any dose that achieves it must be acceptable. $aPLA_2R$ has very good association with clinical activity;[7] in the present report, all the responders had reduction in $aPLA_2R$

Table 1. Clinical and biochemical parameters of all the 6 subjects

S No.	Primary IST	Indication	Baseline UP (g/d)	Baseline Sr Alb (g/dl)	Second *month* completion UP (g/d)	Second *month* completion Sr Alb (g/dl)	Fourth *month* completion UP (g/d)	Fourth *month* completion Sr Alb (g/dl)	Sixth *month* completion UP (g/d)	Sixth *month* completion Sr Alb (g/dl)	F/U (mo)	*Last follow-up* UP (g/d)	*Last follow-up* Sr Alb (g/dl)	*aPLA$_2$R (RU/ml)* Pre-RTX	*aPLA$_2$R (RU/ml)* Post-RTX	*RTX* Additional doses	*RTX* Time (mo)
1	cCTX/GC	Relapse	8.98	3.10	3.88	3.10	3.60	3.20	1.03	3.60	14	0.701	3.70	73.11	4.528	02	03, 08
2	cCTX/GC	Resistant	6.20	1.40	1.20	5.50	1.25	5.20	3.00	2.10	12	3.20	3.10	121.59	93.99	03	01, 04, 05
3	TAC	Intolerant	2.30	1.30	2.90	3.13	2.86	3.42	1.92	4.32	15	0.29	4.32	28.87	2.00	04	04, 09, 12, 15
4	cCTX/GC	Resistant	5.50	3.50	2.90	3.90	3.10	3.20	3.20	4.40	13	1.13	4.34	111.87	2.00	02	02, 06
5	cCTX/GC	Resistant	31.00	1.68	16.220	1.59	3.80	1.98	19.60	1.83	10	8.80	3.50	27.13	79.76	02	01, 04
6	cCTX/GC[a]	Resistant	18.41	1.60	15.03	1.30	9.58	2.63	8.00	2.00	14	3.13	3.30	59.89	56.79	03	02, 05, 06

Mean time to CD19 repletion was 2.17 ± 1.17 (range 1–4) mo and all the subjects received further therapy (median doses 2.5, range 2–4).
aPLA$_2$R, m-type phospholipase A2 receptor antibody; cCTX/GC, cyclical cyclophosphamide and steroids; F/U, follow-up; IST, immunosuppressive therapy; RTX, rituximab; Sr Alb, serum albumin; TAC, tacrolimus; UP, urine protein.
[a]Patient developed upper respiratory tract infection, which was successfully managed with oral antibiotics.

to <20 RU/ml, whereas none of the nonresponders achieved similar titer. Our results support the incorporation of aPLA$_2$R monitoring in the management of difficult to treat PMN.

To conclude, in cost-restrained setting, low-dose RTX targeting CD19 depletion can be used in the management of PMN refractory to standard immunosuppressive therapies with the acceptable side effect profile.

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DISCLOSURE

All the authors declared no competing interests.

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How Well Does Serum Albumin Correlate With Dietary Protein Intake in Dialysis Patients?

To the Editor: Serum albumin is a useful screening tool for recognizing protein energy wasting (PEW) in dialysis patients. However, there are many nonnutritional conditions that are far more important determinants of serum albumin levels than a patient's nutritional state.[1,2] Nevertheless, we have observed that it is not unusual for caregivers to make a reflex connection between serum albumin and dietary protein intake and to act on an unfounded belief that protein